REMARKS

Claims 1-5 and 20-22 are pending and under examination in the subject application. Applicants have canceled claims 1-3, 5 and 20-22 without disclaimer or prejudice to their right to pursue the subject matter of thee claims in the future. Applicants have also amended the specification to fully describe the Penetratin® product already described and to insert a new Sequence Listing. Applicants note that Penetratin® is manufactured by Qbiogene, Inc. of Irvine, CA, and that the amino acid sequence of Penetratin® was known in the art at the time the subject application was filed. In support of this position, applicants attach as **Exhibit B** hereto a printout from Qbiogene's website for describing their Penetratin™ 1 product. Applicants also attach as **Exhibit C** hereto a copy of Bonfanti, et al. ("$p21^{WAF1}$-derived Peptides Linked to an Internalization Peptide Inhibit Human Cancer Cell Growth, Cancer Res. 57, 1442-1446 (1997)), which is listed on the Qbiogene webpage as a reference describing Penetratin™ 1. Applicants note that page 1443 of Bonfanti, et al. disloses the 16 amino acid sequence of Penetratin™ 1. Claim 4 has also been amended to more particularly point out the subject matter which applicants regard as their invention. Support for the amendment to claim 4 can be found in the specification at, *inter alia*, page 9, lines 12-15; page 11, line 34 to page 12, line 3; page 15, line 33 to page 16, line 2; and Figure 4B. Applicants maintain that these amendments raises no issue of new matter. Accordingly, upon entry of this Amendment, claim 4, as amended, will be pending and under examination.

Rejection under 35 U.S.C. §112, First Paragraph

The Examiner rejected claims 1-5 and 20-22 under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter not described in the specification in such a way as to enable one skilled in the relevant art to make or use the claimed invention. Applicants note that claim 4 has been amended herein.

In response to the rejection of claim 1-3, 5 and 20-22, applicants note that these claims have been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to this ground of rejection as it might be applied to amended claim 4, applicants respectfully traverse.

Specifically, the Examiner alleges that the specification fails to disclose any particular function or biological significance for the CD44-ICD polypeptide. Applicants note that the CD44-ICD polypeptide corresponds to the soluble domain of CD44 having a molecular weight of about 14 to 17 kDa recited in amended claim 4.

The Examiner also alleges that it is not the CD44-ICD fragment that is associated with the observed growth inhibition induced by hyaluronan (HA), but rather the soluble CD44 fragment. The Examiner further alleges that the specification describes the use of the γ-secretase inhibitor, Compound E, and not the CD44-ICD fragment to show the importance of CD44-ICD in growth inhibition induced by HA.

In response, applicants maintain that the soluble domain of CD44 protein having a molecular weight of about 14 to 17 kDa, i.e., CD44-ICD, does possess a particular function or biological significance. Applicants note that the Examiner erroneously states on page 3 of the specification that it is not CD44ICD, but rather the soluble CD44 fragment that is associated with growth inhibition. Applicants direct the Examiner's attention to page 16, lines 1 and 2 of the specification which identifies CD44-ICD as a soluble intracellular domain of CD44.

Applicants further direct the Examiner to the paragraph beginning on page 17, line 1. This paragraph states, in relevant part, that:

1. High molecular weight forms of HA induce cell growth arrest;

2. Treatment of cells with high molecular weight forms of HA leads to the generation of CD44-ICD in a γ-secretase-dependent manner;

3. HA treatment induced growth inhibition in cells transfected with CD44; and

4. Treatment of Compound E, a γ-secretase inhibitor, reverted the growth inhibition induced by HA.

Accordingly, applicants maintain that γ-secretase-mediated cleavage of CD44, i.e., production of CD44-ICD, which is associated with the observed growth inhibition induced by HA, is actually attributable to CD44-ICD.

Applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §112, first paragraph.

Rejections under 35 U.S.C. §102

The Examiner rejected claims 1-4 under 35 U.S.C. 102(a) as allegedly anticipated by Okamoto, et al. (2001).

In response to the rejection of claim 1-3, applicants note that these claims have been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to this ground of rejection as it might be applied to amended claim 4, applicants respectfully traverse.

M.P.E.P. §2131 states that a "claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." (citing *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Applicant asserts that Okamoto, et al. (2001) fail to teach each and every element of the claimed invention.

Specifically, nowhere does Okamoto, et al. (2001) teach a composition comprising a 16 amino acid polypeptide having an amino acid sequence as set forth in SEQ ID NO:2 which is from an Antennapedia protein of a *Drosophila* fruit fly.

Accordingly, applicants respectfully request that the Examiner

reconsider and withdraw the rejection under 35 U.S.C. §102(a).

The Examiner also rejected claims 1 and 2 under 35 U.S.C. §102(b) as allegedly anticipated by Okamoto, et al. (1999) and evidenced by Okamoto, et al. (2001).

In response, and without conceding the correctness of the Examiner's rejection, applicants note that claims 1 and 2 have been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

Rejection under 35 U.S.C. §103(a)

The Examiner rejected claims 1, 4 and 5 under 35 U.S.C. §103(a) as allegedly obvious over Okamoto, et al. (1999) or Okamoto, et al. (2001), each in view of U.S. Patent No. 5,968,824 ("the '824 patent").

In response to the rejection of claims 1 and 5, applicants note that these claims have been canceled herein. Accordingly, the Examiner's rejection thereof is moot.

In response to this ground of rejection as it might be applied to amended claim 4, applicants respectfully traverse.

Specifically, the Examiner alleges that Okamoto, et al. (2001) teach that following cleavage of CD44, CD44-ICD translocates into the nucleus of a cell. Based on this observation, the Examiner alleges that it would have been obvious to one skilled in the art

at the time the invention was made to link the CD44 fragment taught by Okamoto, et al. (2001) or to substitute the HA tag of CD44-ICD with Penetratin® peptide as taught by the '824 patent to facilitate transport of the CD44 fragment or CD44-ICD through a cell membrane.

To establish a *prima facie* case of obviousness, the Examiner must demonstrate three things with respect to each claim. First, the cited references, when combined, must teach or suggest each element of the claim. Second, one of ordinary skill would have been motivated to combine the teachings of the cited references at the time of the invention. And third, there would have been a reasonable expectation that the claimed invention would succeed. The Examiner has failed to do this.

Applicants direct the Examiner's attention to the printout of the Penetratin™ 1 product from the Qbiogene website (**Exhibit B**). Specifically on page 2 of the printout, various applications for Penetratin™ 1 are listed. Nowhere is there a teaching or suggestion to use Penetratin for the internalization of a soluble intracellular domain of a receptor. Accordingly, it would not have been obvious for one skilled in the art to combine the teachings of the references cited by the Examiner to obtain the invention defined by amended claim 4.

Accordingly, applicants respectfully request that the Examiner reconsider and withdraw the rejection under 35 U.S.C. §103(a).

Supplemental Information Disclosure Statement